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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/761,435	01/22/2004	Pablo Umana	1975.0180003/TJS	3728

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EXAMINER	
BURKHART, MICHAEL D	
ART UNIT	PAPER NUMBER
1633	
MAIL DATE	DELIVERY MODE
01/21/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/761,435	UMANA ET AL.	
	Examiner	Art Unit	
	Michael Burkhart	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *30-34,65-68,73,74,82-95,186,188-190,195 and 206-212* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30-34, 65-68, 73, 74, 82-95, 186, 188-190, 195, 206-212* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/26/2009 has been entered.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 30-34, 65-67, 73, 74 and 82-95 are rejected under 35 U.S.C. 102(b) as being anticipated by Umana et al (WO 99/54342, cited by applicants, IDS of 5/23/2008) as evidenced by Grabenhorst et al (1999, JBC) and Shields et al (JBC, 2002, of record).

Umana et al teach mammalian cell lines (i.e. CHO hamster cells) modified to express the GnT III enzyme as a fusion protein with various tags, such as GFP or myc-tags, along with various IgG molecules. See pages 27-28, 34-38, and 44. Umana et al teach the GnTIII is a Golgi enzyme, and that β(1,4)-galactosyltransferase (GalT) competes with GnTIII in the Golgi for certain substrates (e.g. page 39). Grabenhorst et al reinforce this, and teach that GnTIII and GalT inherently have Golgi localization domains (see Fig. 2, Table I and page 36110, second

column, first full ¶ of Grabenhorst et al in particular). Umana et al teach that in order to improve the glycosylation pattern of antibodies for increased ADCC, it would be desirable to re-distribute the GalT enzyme by exchanging its transmembrane domain (i.e. its localization domain) with that of another enzyme found in the trans Golgi network, e.g. α2,6-sialyltransferase, such that GalT would be further removed from competition with GnTIII for substrates (see also Figs 10 and 11, illustrating the pathway at issue, and how GalT and GnTIII compete for, at least, the M_3Gn_2 substrate). See pages 38-39. Thus, the α2,6-sialyltransferase/GalT fusion protein anticipates the fusion protein recited in claims 30, 31 and 65. This fusion protein would necessarily have the fusion domain of GalT, as that is the rationale behind this modification, i.e. to remove the GalT catalytic function from that of GnTIII.

The antibodies of Umana et al may be IgG1 which inherently have an Fc region, absent evidence to the contrary (page 31, last ¶). The antibody molecules expressed may be fusion proteins having an Fc region (page 24). The antibodies produced in the CHO-GnTIII cell lines had increased Fc-mediated cellular toxicity, or ADCC (page 38), linked to the increased expression of GnTIII. Umana et al teach that ADCC is mediated by FcγRs (page 21), and that there was an increase in bisected, complex oligosaccharides in the Fc region (page 9). Umana et al teach that expression of GnTIII reduces the amount of bisected, hybrid fucosylated oligosaccharides (page 38) because oligosaccharides modified by GnTIII are no longer substrates for fucosylation. Thus, in relation to antibodies produced in unmodified CHO cells, which do not express significant levels of GnTIII (page 9), the methods of Umana et al using GntIII expression in CHO cells is considered to have resulted in an increased proportion of nonfucosylated oligosaccharides relative to antibodies produced in unmodified CHO cells.

Shields et al teach this lack of fucosylation inherently leads to an increase in FcγRIIIA affinity. Furthermore, at least one type of non-fucosylated bisected, complex oligosaccharide (m/z 1705, Figs 10 and 11) was found in an increased proportion in CHO cells expressing GnTIII (Fig. 9C, D, or E) relative to Sp2/0 cells (Fig. 9A). Regarding claims 92-95, the results of Umana et al indicate that up to 45-50% of the glycans are bisected, non-fucosylated upon expression of GnT-III (page 37, and Figures 9-10).

Regarding claim 83, the instant specification (¶ [0031] of the published application) teaches FcγRIIIA to be an activating receptor.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 30-34, 65-68, 73, 74, 82-95, 186, 188-190, 195 and 206-212 are rejected under 35 U.S.C. 103(a) as being unpatentable over Umana et al (WO 99/54342,) Grabenhorst et al (1999,

JBC) and Shields et al (JBC, 2002, of record) in view of Russell et al (WO 01/29242 A2, 2001) and Rabouille et al (1995, J. Cell Sci., cited by applicants).

Umana et al teach mammalian cell lines (i.e. CHO hamster cells) modified to express the GnT III enzyme as a fusion protein with various tags, such as GFP or myc-tags, along with various IgG molecules. See pages 27-28, 34-38, and 44. Umana et al teach the GnTIII is a Golgi enzyme (e.g. page 39); Grabenhorst et al reinforce this, and teach that it inherently has a Golgi localization domain (see Fig. 2, Table I and page 36110, second column, first full ¶ of Grabenhorst et al in particular). The antibodies of Umana et al may be IgG1 which inherently have an Fc region, absent evidence to the contrary (page 31, last ¶). The antibody molecules expressed may be fusion proteins having an Fc region (page 24). The antibodies produced in the CHO-GnTIII cell lines had increased Fc-mediated cellular toxicity, or ADCC (page 38), linked to the increased expression of GnTIII. Umana et al teach that ADCC is mediated by FcγRs (page 21), and that there was an increase in bisected, complex oligosaccharides in the Fc region (page 9). Umana et al teach that expression of GnTIII reduces the amount of bisected, hybrid fucosylated oligosaccharides (page 38) because oligosaccharides modified by GnTIII are no longer substrates for fucosylation. Thus, in relation to antibodies produced in unmodified CHO cells, which do not express significant levels of GnTIII (page 9), the methods of Umana et al using GntIII expression in CHO cells is considered to have resulted in an increased proportion of nonfucosylated oligosaccharides relative to antibodies produced in unmodified CHO cells. Shields et al teach this lack of fucosylation inherently leads to an increase in FcγRIIIA affinity. Furthermore, at least one type of non-fucosylated bisected, complex oligosaccharide (m/z 1705, Figs 10 and 11) was found in an increased proportion in CHO cells expressing GnTIII (Fig. 9C,

D, or E) relative to Sp2/0 cells (Fig. 9A). Regarding claims 92-95 and 209-212, the results of Umana et al indicate that up to 45-50% of the glycans are bisected, non-fucosylated upon expression of GnT-III (page 37, and Figures 9-10).

Regarding claim 83, the instant specification (¶ [0031] of the published application) teaches FcγRIIIA to be an activating receptor.

Regarding claim 186, Umana et al teach that the cells of their invention may also comprise mannosidase II, or Man II, which may be expressed with GnTIII (pages 7 and 13). Absent evidence to the contrary, the GnTIII used by Umana et al has a catalytic domain because it performed the catalytic function of the enzyme for reason set forth above, i.e. it added the bisecting GlcNAc to oligosaccharides.

Umana et al suggest that in order to improve the glycosylation pattern of antibodies for increased ADCC, it would be desirable to re-distribute the GalT enzyme by exchanging its transmembrane domain (i.e. its localization domain) with that of another enzyme found in the trans Golgi network, e.g. α2,6-sialyltransferase, such that GalT would be further removed from competition with GnTIII for substrates (see also Figs 10 and 11, illustrating the pathway at issue, and how GalT and GnTIII compete for, at least, the M_3Gn_2 substrate). See pages 38-39. Furthermore, Grabenhorst et al teach the routine modification of Golgi-resident enzymes by replacement of the localization domain, or CTS, with those of another. See the abstract, Fig. 2, and Table I in particular. Grabenhorst also teach that mannosidase II and GnTI (*medial* Golgi) are located before GalT in the Golgi network (abstract, top of column 2, page 36107), and that GnTIII is located after GnTI, but before GalT.

None of Umana, Grabenhorst or Shields et al teach the use of the Man II CTS to modify the GnTIII enzyme.

Russell et al teach modifying the glycosylation of heterologous proteins, such as antibodies, by expression of fusion proteins comprising a post-translational modification enzyme and the "CMS" region of glycosyltransferases or hydrolases located at a desired point in the glycosylation pathway. The CMS region is taught to be the region that determines spatial distribution of a protein in the ER and/or Golgi, and is considered an synonym for the term "CTS" used by Grabenhorst et al. See Example 3, beginning on page 69. Russell et al disclose that post-translational modification enzymes include the general use of N-acetylglucosaminyltransferases (page 8, last ¶) and β-1,4 N-acetylglucosaminyltransferase III (GnT-III) specifically (page 52, first ¶). CMS regions to be used are from enzymes that prepare the glycans for subsequent fucosyl and xylosyl addition, such as mannosidase II (Mann II). See page 69, line 24 to page 70, first full ¶, and Figure 16.

Rabouille teach that Mann II is a *medial* Golgi enzyme that occurs in the ER/Golgi pathway prior to the *trans* Golgi and *trans*-Golgi network enzyme GalT. See the abstract and Introduction on page 1617.

The claimed method of modifying a glycosylation profile is essentially disclosed by Umana et al with the exception of using a Mann II CTS domain in fusion with the GnTIII enzyme in order to relocate the GnTIII in the Golgi pathway. The ordinary skilled artisan, seeking a method to modify the glycosylation profile of antibodies for increased ADCC, would have been motivated to use a Mann II CTS in a fusion polypeptide with GnTIII because Umana et al teaches the desirability of locating GnTIII before GalT in the Golgi pathway, and suggests

relocation of one of these enzymes (GalT) after GnTIII in the pathway by replacing the native GalT CTS with that of a later enzyme in the pathway. The teachings of Russell et al regarding the use of a heterologous CTS to modify the location of glycosylation enzymes in the Golgi pathway, coupled with the teachings of Rabouille and Grabenhorst et al regarding the location of Mann II prior to GalT in the Golgi pathway present an obvious alternative solution to relocating GnTIII prior to GalT in this pathway. It would have been obvious for the skilled artisan to do this because of the known benefit of generating increased ADCC by glycosylation modification as taught by Umana et al. Given the teachings of the cited references and the level of skill of the ordinary skilled artisan at the time of applicants' invention, it must be considered, absent evidence to the contrary, that the ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Response to Arguments

Applicant's arguments filed 10/26/2009 have been fully considered but they are not persuasive. Applicants essentially assert that: 1) Umana et al only teach that it might be desirable to redistribute glycosyltransferases if certain structures are found to increase ADCC activity, and that there is no suggestion by Umana et al to move GalT to the medial-Golgi; 2) Grabenhorst et al do not teach moving GalT or GnTIII to the medial Golgi and thus does not cure the deficiencies of Umana et al, Grabenhorst et al does not provide any teaching or suggestion to modify GalT or GnTIII by adding the localization domain of ManII, and there is no reasonable expectation of success when combining Umana and Grabenhorst et al; 3) Shields et al do not teach the redistribution of GalT or GnTIII and thus does not cure the deficiencies of Umana et al, and there is no reasonable expectation of success when combining Umana, Grabenhorst and

Shields et al; 4) Russell et al is directed to plant cells whereas the instant claims require mammalian cells and thus does not cure the deficiencies of Umana et al, Russell et al teaches away from the instant invention, and there is no reasonable expectation of success when combining Umana, Grabenhorst, Russell and Shields et al; 5) Rabouille et al do not teach the redistribution of GalT or GnTIII and thus does not cure the deficiencies of Umana et al, and there is no reasonable expectation of success when combining Umana, Grabenhorst, Russell, Rabouille and Shields et al; 6) the teachings of Ferrara et al show that redistribution of GnTIII results in an increased proportion of bisected non-fucosylated hybrid oligosaccharides.

Regarding 1), this is a limited view of the teachings of Umana et al (and of the totality of the prior art cited in this rejection), and applicants provide no support (in the form of page numbers and line numbers) where these alleged teachings can be found in Umana et al. In contrast, the Examiner has provided specific reference to pages and figures outlining the suggestion of Umana et al to modify the localization domain of the GalT enzyme such that it is removed from the GnTIII enzyme. The teachings of Umana et al are not limited to modifying GalT such that it is found in the trans-Golgi, as applicants appear to insist. Umana et al make a broad suggestion that removing GalT to a location after GnTIII in the pathway is desirable in order to decrease competition of these two enzymes for substrates, and suggest α2,6-sialyltransferase (a trans-Golgi enzyme) as an example. Taken with the teachings of the totality of the prior art (which applicants ignore throughout the instant response, as each piece of art is discussed piecemeal), modifying GnTIII to be a medial-Golgi enzyme is an obvious alternative to modifying GalT: it accomplishes the same goal of moving GnTIII to a location in the pathway that is prior to GalT.

Regarding 1) - 5), in response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Further regarding 2), Grabenhorst do teach the localization of FT-6 to the medial Golgi, as all of the CTS regions used in the fusion proteins are not trans or TGN-localized proteins as applicants insist. Grabenhorst et al teach the ManII and GnTI are medial Golgi enzymes (page 36107, the top of the second column) then go on to prepare a fusion protein comprising GnTI CTS and the FT6 catalytic domain (e.g. Fig. 2 and Table I).

Further regarding 2) - 5), applicants unsupported assertions that there is no reasonable expectation of success when combining the references are less than convincing in light of the reasoning provided by the Examiner and the extensive teachings provided by the prior art of record. "Argument of counsel cannot take the place of evidence lacking in the record." In re Scarbrough, 182 USPQ 298, 302 (CCPA 1974).

Further regarding 4), Russell et al is not relied upon to teach mammalian cells, and given the preponderance of references that teach the use of mammalian cells (all of the other references in this rejection, at the least) when using the claimed methods, it is not convincing that Russell et al "teaches away from" the combination of the instant references. It is clear from the totality of the prior art that mammalian cells are desirable for use in the claimed methods. Also see, for example, Andersen et al (2002, Cur. Opin. Biotech., cited by applicants) and Chadd et al (2001, Cur. Opin. Biotech., cited by applicants). Finally, Russell et al was only relied upon to teach modification of the location of glycosyltransferases in the Golgi when modifying the

glycosylation patterns of antibodies. It was not used as a reference to teach the use of mammalian cells.

Regarding 6), the teachings of Ferrara et al are stipulated, but, applicants do not explain (and it is not entirely clear), how these teachings mitigate against the instant rejection. It is also noted Ferrara et al was published in 2006, and the instant application seeks a priority date of 2003. Ferrara et al thus cannot provide a reason to combine the above references as of applicants filing date, or the date of the references.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Burkhart whose telephone number is (571)272-2915. The examiner can normally be reached on M-F 8AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael Burkhart/
Primary Examiner, Art Unit 1633